REMARKS

Claims 9-29, 32-37, 48-111 have been canceled solely to comply with the formality to cancel non-elected claims. Claims 1, 38, 41-47, 112, 113 have been amended. Support for the claim amendments can be found throughout the instant application including the Drawings and claims as filed originally.

For instance, particular support for the amendments to claim 1 can be found at pg. 6, lines 19-25; pg. 10, lines 12-23; pgs. 28-29, bridging paragraph, and the example section.

As an initial matter, Applicants respectfully request that the USPTO withdraw the finality of the instant Action pursuant to MPEP §706.07(a). In particular, the Rack and Rowen references are newly cited art that have been applied against claims that have not been amended by applicant. See, for instance, claims 2 and 39 (originally filed). These have not been amended to require newly cited art under MPEP §706.07(a). Accordingly, it is submitted that the finality of the instant action is improper and should be withdrawn. Such action is respectfully requested.

As a further initial matter, Applicants request consideration of the Information Disclosure Statement filed on May 16, 2005. A copy of the Information Disclosure Statement By Applicant is attached to this submission. If the Examiner requires a copy of any (or all) of the cited references, the undersigned will promptly provide copies on request.

The Action notes that the pending claims have been examined insofar as they encompass the elected species. Applicants expect that prior to an allowance of the pending claims, the Office will conduct a full and thorough search of the literature commensurate with the scope of those claims.

Objections To Claims 38, 41, and 42-47

Claims 38 and 41 stand objected to as not satisfying various formalities. The claims have been amended to satisfy those concerns. The Examiner's attention to this typographical oversight is appreciated.

Regarding claims 42-47, the amendments requested by the Examiner at pg. 3 have been made including canceling claim 40

Rejection of Claims Under § 103(a)

Claims 1-2, 5, 708, 30-31, 38-45 stand rejected as being unpatentable over USP No. 5,859,312 to Littman in view of Mombaerts, McMurry, Rowen and Rack as cited in the Action. Applicants respectfully disagree with the rejection especially in view of the present claim amendments.

As cited, Littman is said to teach methods for producing transgenic mice that express T-cell receptor alpha and beta gene products (citing '312 at columns 8-9). Littman is also relied on as providing disclosure relating to making transgenic mice with the gene products and that have inactivated cognate lymphocyte transduction transgenes. Action at pg. 5. Applicants note that Littman discloses that it is "generally preferable" to join a lymphocyte transduction encoding sequence to transcriptional regulatory elements which *naturally occur* in or near the cognate lymphocyte transduction gene. Littman at Col. 7, lines 4-10.

Moreover, the Littman patent provides experimental data showing that using heterologous regulatory elements to drive expression of at least one lymphocyte transduction transgene (CD4) will result in abnormal and undesirable expression. See Col. 32, lines 15-22 reproduced below.

In particular, Col. 32, lines 15-22 of the Littman patent provides:

EXAMPLE 2

> **Previous attempts by others to achieve appropriate expression of CD4 transgenes in mice have not been successful. Use of heterologous T cell-specific enhancers and promoters has resulted in the expression of CD4 in thymocytes and in T cells which do not normally express this protein, such as mature CD8.sup.+ cells, as well as inappropriate levels of CD4 expression.**

Accordingly, the Littman patent clearly instructs the reader to use *endogenous* murine regulatory sequences to drive expression of human lymphocyte transduction transgenes when expressed in transgenic mice. Constructs with heterologous sequences may not work according to Littman.

In marked contrast, Applicants have shown that it is possible to make unrearranged human T-cell receptor loci under the control of human T-cell receptor loci regulatory sequences. That is, it was found that the human regulatory sequences driving expression of the loci will work well in mice. See, for instance, Examples 4-5a, 5b (how to make large human TCR alpha and beta transgene constructs with homologous (human) regulatory sequence), and Examples 6-8 (how to produce transgenic mice with the TCR transgenes). See also the Declaration of Heather Belmont (of record), particularly at ¶6, in Belmont stated that the transgenic mice of the invention include human regulatory elements (promoters, enhancers, splice sites, poly A sites and others) are functional in mice.

Accordingly, Littman as cited by the Office would clearly dissuade one from making and using the presently claimed invention on grounds that the human regulatory elements would not drive expression of transgenes sufficiently in mice. None of the other cited references remedy this defect. None of the other references as relied on teach or suggest which of the lymphocyte transduction transgenes disclosed by the Littman patent, if any, would work in association with human regulatory sequences and which would not work.

Thus on this basis alone, the Office has not made a *prima facie* case of obviousness

and the rejection should be withdrawn.

Applicants respectfully disagree with the ¶103 rejection on further grounds.

For instance, the Office took the position that the nucleic acids of Rowen and Rack could be used to make transgenic mice as suggested by Littman. As cited, the nucleic acids are understood to include *human regulatory elements*. Yet according to Littman, transgenes bearing heterologous regulatory sequence will not work in mice at least for some transgenes. See Col. 32, lines 15-22 for instance. Accordingly, a worker with knowledge of Littman as cited would be dissuaded from using the nucleic acids taught by Rowen and Rack on grounds that to do so would not produce desired transgenic animals. On this basis alone, the instant *prima facie* case of obviousness cannot stand.

Additionally, it is apparent from the rejection that the Office understood Littman to teach that a worker could readily make a transgenic mouse in which endogenous lymphocyte transduction proteins are inactivated and cognate human proteins are made. However, this is not the case at all in view of the cited art. For instance, even Littman admits that others in the field failed to make CD4 transgenes in mice. Col. 32, lines 15-18. Thus it is not clear from Littman taken alone or in combination with the other cited references that it would be obvious to make animals that express unrearranged T cell alpha and beta loci. Applicants' specification provides clear and unambiguous guidance that such constructs could be made. It is respectfully suggested that the Office has read too much from Littman and that in view of the reference itself, it was not obvious that transgenic mice encoding some transgenes could be made. Accordingly, and on this basis alone, the *prima facie* case cannot stand.

Turning to Mombaerts, Applicants respectfully submit that it is not an enabling reference for the purpose it is being used in the rejection. As such, it should be withdrawn as

a prior art reference.

More specifically, Mombaerts is relied on as evidence that at the time Applicants filed their application, transgenic mice were available that expressed unrearranged human T cell receptor loci and mice with deletions in endogenous TCR. Action at pg. 6. However, a fair reading of Mombaerts does not support this position. In particular, pg. 280, col. 2 of the reference (under "Experimental Procedures" and "Mice") provides little specific guidance on how to make and use TCR alpha and TCR beta mutant mice. According to Mombaerts, five strains of TCR mice "will become available from The Jackson Laboratory, Bar Harbor Maine in early 1994." This statement implies that Mombaerts viewed the cited TCR deficient mice as being sufficiently difficult to make and use to warrant submission to a commercial depository. There is no indication on record that these mice were ever available to the public as of the date of the cited reference or at any other time.

Thus, Mombaerts as cited is not an enabling reference as it does not show how to make and use the mice strains referenced in the rejection. None of the other references taken individually or in combination show how to make and use the cited mice strains from Mombaerts. Since Mombaerts is not an enabling reference as relied on, it should be withdrawn and the rejection reconsidered.

Turning to the Office Action, Applicants respectfully request clarification regarding the discussion of Figure 1. Respectfully, there is no pg. 3085 in Mombaerts and Figure 1 does not show deletion of genes as alleged in the Action.

McMurry is cited as supplementing Littman by teaching transgenic mice carrying the human unrearranged TCR delta gene minilocus. Transcriptional regulatory elements are understood to be human. See, for instance, the Abstract and pg. 4554, col. 1. However as

already discussed, Littman disclosed that at least some constructs require endogenous (murine) transcription regulatory elements. See, for instance, the '312 patent at Col. 32, lines 15-22. Thus, a worker in the field would be dissuaded from combining McMurry and Littman in the way suggested by the Office on grounds that the transgenes would not be expressed sufficiently. For this reason alone, the Office has not made a *prima facie* case for obviousness and the rejection should be withdrawn.

Applicants respectfully disagree with the ¶103 rejection on further grounds.

For instance, McMurry is understood to disclose transgenic mice resulting from the production of non-functional T-cell receptor constructs. That is, McMurry's constructs were made with the goal of studying TCR gene arrangements and not generation of functional T-cell receptor. This understanding is borne out by the disclosed minilocus constructs. As cited by the Office, they are artificial and inactivated constructs. As understood, McMurry's minilocus was generated by a strategy of stepwise cloning of selected DNA fragments of the human TCR delta locus. The V-delta-1 and V-delta-2 gene elements used in the generation of McMurry's transgenic mice are said to have mutations that destroy the V element open reading frames and prevent a rearranged transgene from encoding a functional TCR protein. See McMurry at pg. 4554 (i.e. references 20, 27, 28 and 29) and Figure 1. Applicants believe these manipulations were done to minimize functional expression of the transgenic TCR that apparently could influence thymic development (see reference 27 and 28). Thus, in contrast to the rejection position, McMurry certainly does not teach that transgenic mice comprising an unrearranged human TCR locus could productively rearrange and produce expression of detectable amounts of transgenic TCR.

None of the other references remedy this deficiency. Accordingly, the Office has not made a *prima facie* case that could withstand scrutiny. For this reason alone, the rejection

should be withdrawn.

In addition, Applicants note that many of the transgenic mice disclosed by McMurry apparently not publicly available at the time the reference was published. See, for instance, pg. 4554 under "Materials and Methods" where the authors disclose only that mouse lines A, H, J, P, Q, U, and Z were described "previously". That is not an enabling disclosure. For example, it is not clear how to make and use the cited mice strains nor provide any indication about how (or if) the public can access the strains.

Further, the transgenic mice of McMurry as cited carry only a single transgenic TCR locus. That is, the mice are not said to carry the human TCR gamma or beta loci. These elements are normally required for making fully heterologous TCR protein. None of the other cited references, taken alone or in combination, teach, suggest or provide any motivation to add the human TCR gamma or beta locus to any transgenic mouse carrying the human TCR delta locus to generate a transgenic animal capable of producing heterologous T-cell receptors.

Furthermore, neither McMurry nor Littman disclose generation of transgenic mice containing unrearranged human TCR alpha and beta loci or generation of transgenic mice expressing functional human TCR containing alpha and beta chains.

For all these reasons, citation of McMurry does not support the instant prima facie case. Reconsideration and withdrawal of the obviousness rejection are requested.

Applicants disagree with the ¶103 rejection on still further grounds.

For instance, Rack as cited is not an enabling reference. As such, it should be withdrawn as a reference. In particular, nowhere does the reference disclose how to make and

use any YAC containing 70% of the TCR alpha locus (with multiple TCR alpha V genes and other elements) as alleged in the Action at pg. 6. See Rack at pg. 1234, col. 1 (disclosing use of a YAC library made by another to produce a 900kb construct). Accordingly, the instant *prima facie* case cannot stand on grounds that Rack is not an enabling proper prior art reference to the extent it is relied on in the rejection.

Moreover, even if a worker was somehow able to obtain the Rack YAC referenced by the Office, there is no indication from Rack or the other cited references how many TCR J gene segments are within the YAC (only one J-alpha label is shown in Figure 1). Rack merely discloses use of the TCR alpha/delta locus YAC as a probe to detect chromosomal abnormalities and not as a functional transgene for producing transgenic animals. Rack describe the TCR alpha/delta locus as unusual insofar as the TCR delta genes are situated within the TCR alpha locus (page 1233 first column). Thus, a worker would be dissuaded from using Rack's YAC construct (if it could be obtained at all) to make transgenic mice as taught by Littman. None of the other references remedies this defect. Reconsideration and withdrawal of the rejection on this basis alone is requested.

In addition, the Office maintains that Rowen and Rack supposedly supplement Littman by teaching the complete 685-kb DNA sequence of the human beta TCR locus and a YAC containing 70% of the TCR alpha locus including multiple TCR alpha V genes, all of the J genes and the C alpha genes respectively. However, neither Rowen nor Rack provide any description or motivation for the use of the human TCR loci as transgenes to generate the transgenic animal of the invention.

In view thereof, Applicants respectfully submit that the Office has not made a *prima facie* case of obviousness. Reconsideration and withdrawal of the rejection are thus requested, particularly in view of the present claims.

Rejection Under 35 USC 112, second paragraph

Claims 1-2, 4-7, 30 and 31 stand rejected as being indefinite for reciting "human alpha and beta chains". While Applicants respectfully disagree with the position taken, basis for the rejection has been addressed by this submission.

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

Applicants believe that additional fees are not required in connection with the consideration of the within matter. However, if for any reason a fee is required, a fee paid is inadequate or credit is owed for any excess fee paid, you are hereby authorized and requested to charge Deposit Account No. **04-1105.**

Respectfully submitted,

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	10/024,648-Conf. #2636
Filing Date	December 19, 2001
First Named Inventor	Heather J. Belmont
Art Unit	1632
Examiner Name	A. M. S. Wehbe
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U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	B1	WO 97/32603 A	09-12-1997	Scripps Research Institute		

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NON PATENT LITERATURE DOCUMENTS

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	C1	ROTHE JOACHIM, et al., "Functional expression of a human TCR-beta gene in transgenic mice" International Immunology, Vol. 5, No. 1, 1993, pp. 11-17, XP009039278, ISSN 0953-8178.	
	C2	VINEY J. L., et al., "Generation of monoclonal antibodies against a human T Cell receptorbeta chain expressed in transgenic mice" Hybridoma, Liebert, New York, NY, US, Vol. 11, No. 6, December 1, 1992, pp. 701-713, XP002062863, ISSN 0272-457X.	
	C3	FUKUI YOSHINORI et al., "Differential requirement of MHC class II Molecules expressed on hematopoietic cells for positive selection of CD4+ thymocytes in TCR-alpha-beta and TCR-beta transgenic mice" International Immunology, Vol. 9, No. 9, 1997, pp. 1385-1391, XP002303910, ISSN 0953-8178.	
	C4	CHUNG S. et al., "Functional three-domain single-chain T-Cell receptors" Proceedings of the National Academy of Sciences of USA, National Academy of Science. Washington, U.S., Vol. 91, No. 26, 20 December 1994, pp. 12654-12658, XP002039051, ISSN 0027-8424.	
	C5	ISHIMOTO et al., "In vitro and in vivo evidence for high frequency of I-Ab-reactive CD4+ T cells in HLA-DQ or HLA-DRA transgenic mice lacking endogenous MHC class I and/or class II expression" Journal of Immunology (Baltimore MD), 15 October 1997, Vol. 159, No. 8, pp. 3717-3722, XP002303911, ISSN 0022-1767.	

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